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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	PAPER NUMBER
1636	10

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,392	FORD ET AL.	
	Examin r	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/31/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-81* is/are pending in the application.

4a) Of the above claim(s) *21-76* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20 and 77-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *14* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 3/31/03 as Paper No. 15, in which several of the claims were amended (claims 1, 9-11). Claims 1-81 are pending in the instant application, with claims 21-76 withdrawn from consideration as being directed to nonelected inventions.

This action is not final because claim 4 was inadvertently left out of the obviousness rejection in the previous office action. Also, the examiner did not make entirely clear how the references were to be combined in making the obviousness rejection. The examiner has considered applicants' response to this rejection in full, but these arguments were found to be non-persuasive for reasons outlined below.

Information Disclosure Statement

Receipt is acknowledged of an information disclosure statement (IDS) filed 3/31/03 as Paper No. 14. The signed and initialed PTO Form 1449 has been mailed with this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in that the metes and bounds of the phrase "mathematically significant difference between the two groups of animals" are not clear. Just how different does the level of infection, etc., have to be between the two groups in order for it to be considered "mathematically significant"? **This is a new rejection, necessitated by applicants' amendment of claims 1 and 9-11 in Paper No. 15.**

Response to Arguments

In Paper No. 15, applicants' present arguments as to why the term "mathematically significant" should not be considered as vague and indefinite. This includes citing a passage from the application as well as citing three prior art references (see the references cited in the IDS of Paper No. 14). The recited passage from the specification merely indicates that one of skill in the art can determine mathematically significant differences between the two groups, but does not indicate what degree of difference will satisfy the claim limitation. The references cited by the response do not appear to calculate a "mathematically significant" difference between control and test populations in a common fashion. Moreover, the sections from these references cited in the response don't even appear to provide a calculation for "mathematically significant" differences between test and control populations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The claimed invention is drawn towards a process to allow characterization of a microbial gene with regard to its importance in the ability of the microbe to initiate or sustain infection. The method utilizes a tetracycline-responsive promoter (the TCE) to drive expression of a polynucleotide such that the amount of a target gene product encoded by one of the microbial genes is regulated by the presence or absence of tetracycline. A genetically altered microorganism comprising the TCE is used to infect at least two or more mammals at the same time that the animals are exposed to tetracycline such that the function of the targeted microbial gene is regulated. Tetracycline is then removed from a portion of the population of mammals. The degree of infection, number of microbes (i.e. microbe levels) and physiological condition of the mammals is determined for both sets of infected animals (i.e. +/- tetracycline) and the results compared to one another. A "meaningful difference" between the two groups of infected animals indicates the identification of a gene that is important to a microbe's ability to infect, or sustain infection of, a mammal. The tet-responsive promoter can be a prokaryotic promoter. The "meaningful difference" can be a "mathematically significant difference" (although neither term is clearly defined in the specification and claims 9-11 thus read on any quantifiable

difference in pathogenicity between the two groups of infected animals). The host mammals can be mice. The microbes can be recombinant bacteria, a virus or yeast. Specifically, the microbe can be Staphylococcus aureus. The Bostian et al reference of the following rejection teaches each of the above limitations, including the removal of the inducer (i.e. tetracycline) to regulate the target gene function, but does not explicitly teach the use of control animals. The Setterstrom et al reference teaches the use of control animals to provide a clear standard for microbial infection for comparison to test animals where microbial infection has been altered due to interference with at least one gene function (e.g. through the use of antibiotics). Any of the putative essential genes operatively linked to a tetracycline-regulatable promoter taught by Bostian et al whose expression is correlated with a change in infection is necessarily a "reporter" gene in that the effects of its expression is correlated with a specific effect.

Claims 1-4, 6, 8-20 and 77-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bostian et al (WO 96/40979, 19 December 1996; see the entire document) in view of Setterstrom et al (U.S. Patent No. 6,309,669 B1; see the entire patent) and further in view of Burnham et al (U.S. Patent No. 5,891,670; see the entire patent) or Nesin et al (Antimicrobial Agents and Chemotherapy; 1990, pages 2273-2276; see the entire reference). **This rejection is maintained for reasons of record in Paper No. 13, mailed 12/31/02 and repeated below. This rejection is hereby extended to claim 4.**

Bostian et al teach methods for evaluating microbial genes as targets for compounds which inhibit the pathogenesis of a microbe, and for evaluating the expected therapeutic effect of compounds which inhibit a reaction of a microbial cell which is related to the expression of a

specific gene (i.e. the "gene target" of the instant invention). The methods utilize recombinant microbes which contain DNA constructs or alterations (i.e. the "switches" of the Bostian et al application) that allow the level of activity of the products of coding regions associated with those constructs or alterations to be controlled by the presence or absence of a specific small molecule or "switching compound" at any of several points in the infection process (e.g. Abstract; page 17, lines 3-21; page 4, lines 4-19). The expression of the coding regions associated with the DNA constructs or alterations is designed to affect the activity of the specific gene target in the microbe while the microbe is in the process of infecting a host organism. The methods comprise infecting an animal or plant model host with a genetically altered microbe where the genetic alteration causes a change in the level of activity of a product of the coding sequence of a putative pathogenesis gene or essential gene in the microbe in response to an environmental change (e.g. exposure to a switching compound) and determining whether the state of infection or condition of the host is changed as a result of altering the level of activity of the target gene or gene product. In some cases the level of activity of the target gene is affected by the administration of the switching compound to the host animal. In other instances, the level of activity of the target gene is regulated by removing or decreasing the concentration of the switching compound (e.g. page 26, lines 14-31; examiner's emphasis added).

The DNA constructs or "alterations" used in the invention taught by Bostian et al comprise repressor/operator pairs used as regulatory "switches" to control expression of a coding sequence that affects the functional activity of the target gene (e.g. Figure 3; page 41 lines 3-29). A preferred switching compound of the system is tetracycline, used in conjunction with a promoter operatively linked to operator sequences (i.e. tetO) that specifically bind to the

tetracycline repressor (tetR) (e.g. page 17, lines 3-21; page 41, lines 3-29; page 54, lines 15-17). A switching compound of the invention can cause a decrease or an increase in the level of activity of a coding sequence, depending upon the type of DNA construct or alteration used (e.g. sense or antisense expressed and the type of repressor/operator construct) (e.g. pages 56-57). The small molecule-responsive "switches" of the invention can be directly linked to an endogenous target gene of interest (e.g. by integration of a switch construct into a bacterial chromosome such that a chromosomal gene is now responsive to the small molecule "switcher") or indirectly linked by a second repressor/operator element (e.g. Figure 3; page 7, lines 1-17; page 29, lines 12-16).

In the methods taught by Bostian et al, the putative pathogenesis gene or essential gene is a valid target if the state of the infection or the physiological condition of the host is altered in response to the change in level of activity of the target gene (e.g. page 5, lines 16-35). Criteria for evaluation in the host include the ability of the microbe to replicate (the test gene expression can be "on" or "off"), the ability to produce specific exoproducts involved in virulence of the organism, and the ability to cause symptoms of disease in the animals (e.g. page 49, lines 14-19). Acceptable mammalian animal models for use in the system include mice, rats, rabbits, dogs, cats and swine (e.g. page 13, lines 24-27; Examples 5-10). Microbes that can be used in the methods described by Bostian et al include bacteria, protozoa, fungi, yeast and viruses. Staphylococcus aureus is a bacterial microbe described as useful in the methods of the invention (page 14, lines 9-14). Bostian et al teach several different specific animal model systems for studying the effects of altering gene expression on infection of a host animal by a microbe (e.g. the Mouse Soft Tissue Model, the rabbit Osteomyelitis model, etc.; see Examples 5-10). Bostian

et al teach that it is desirable to use switching compounds (i.e. antibiotics or antibiotic analogs) to which the genetically altered microbe is resistant in order to avoid confusion over interpretation of the experimental results (e.g. page 18, first paragraph).

Bostian et al do not explicitly teach the use of control animals in their methods where the target gene function in the infecting microbe has not been inhibited (i.e. a "normal" infection control). Bostian et al do not explicitly teach that the genetically altered microbe of their invention necessarily comprises a tetracycline-resistance gene.

Setterstrom et al teach the use of novel burst-free, sustained release biocompatible and biodegradable microcapsules that can be programmed to release their active core (e.g. an antibiotic) for variable durations ranging from 1-100 days in an aqueous physiological environment (e.g. the Abstract). Setterstrom et al teach a set of examples wherein the rabbit osteomyelitis animal model system is used to demonstrate the efficacy of their invention (e.g. Section VII, Examples 1-7 beginning at column 40 and continuing through column 45, line 60). In these examples, Staphylococcus aureus preparations were used to infect the tibial metaphysis of laboratory rabbits (e.g. Example 1). Antibiotic therapy using the compositions of the Setterstrom et al invention was initiated immediately or delayed for 7-days. For each infected animal the infected tibia was harvested and used to determine the extent of infection (e.g. Example 6). Whether treatment was initiated immediately or postponed for seven days post-infection, the experiments were conducted with control animals that were infected with S. aureus and received no antibiotic treatment (e.g. Examples 3 & 4).

The '670 patent teaches the identification and use of a polynucleotide sequence obtained from S. aureus encoding a tetracycline resistance protein (e.g. Example 1, SEQ ID NO: 1).

Nesin et al teach the cloning and characterization of a tetracycline resistance gene obtained from S. aureus that encodes a resistance protein of the tetM class (e.g. Abstract; Figure 2).

It would have been obvious to one of ordinary skill in the art at the time of applicants' invention to modify the methods taught by Bostian et al for the characterization of potential antimicrobial gene targets (e.g. removal tetracycline to control target gene function in a microbe during infection) to include the use of control animals where the activity of the gene target is not inhibited (e.g. where the tetracycline concentration is maintained) because Bostian et al teach it is within the skill of the art to utilize a tetracycline-responsive system to control the level of activity of a gene target in a microbe during the process of infection and because Setterstrom et al teach it is within the skill of the art to utilize a control animal to provide a clear contrast between treatment or nontreatment of infection. One would have been motivated to do so in order to receive the expected benefit, as exemplified by Setterstrom et al, of being able to compare the level of infection in an animal in which no target gene has been inactivated (e.g. the untreated animals of Setterstrom et al) with an animal in which at least one gene function has been altered (e.g. the animals treated with antibiotics as taught by Setterstrom et al). Absent any evidence to the contrary, there would have been a reasonable expectation of success in using a control animal, as taught by Setterstrom et al, in the methods taught by Bostian et al to provide a clear background for comparison of the effects of target gene inactivation.

It would have been further obvious to one of ordinary skill in the art at the time of applicants' invention to modify the genetically-altered microbe taught by Bostian et al to include a gene encoding resistance gene taught by the '670 patent or by Nesin et al because Bostian et al

teach it is within the skill of the art to utilize a genetically altered microbe that is resistant to the antibiotic "switching" compound in the methods of their invention and because the '670 patent and the Nesin et al reference teach antibiotic resistance genes isolated from a microbe that is featured in a preferred embodiment of the Bostian et al methods (i.e. a genetically-altered S. aureus microbe comprising a tetracycline-controlled gene). One would have been motivated to do so, as taught by Bostian et al, in order to avoid complications in interpreting the experimental data upon addition/withdrawal of the tetracycline "switching" compound. Absent evidence to the contrary, and based upon the combined teachings of the cited references, there would have been a reasonable expectation of success in modifying the microbes taught by Bostian et al to include the tetracycline-resistance genes taught by the '670 patent or by Nesin et al and using the modified microbes in the method developed from the combined teachings of Bostian et al and Setterstrom et al.

Response to Arguments

Applicant's arguments filed in Paper No. 15 have been fully considered but they are not persuasive. The response filed in Paper No. 15 essentially argues: 1) the examiner did not make clear in which combination the references are to be combined, 2) the examiner has failed to establish that there is a suggestion or motivation to combine the teachings of the cited references, 3) the examiner has failed to establish that the combined references teach or suggest all of the claim limitations (e.g. control animals where the concentration of tetracycline is removed), 4) the response implies the examiner tries to improperly extend the teachings of Setterstrom et al concerning control animals from a very specific assay to a much different kind of assay as claimed here, 5) the examiner has not shown that the motivation to combine the two references is

in the knowledge generally available to one of ordinary skill in the art and has used impermissible hindsight in making the rejection, 6) neither the Bostian et al or Setterstrom et al reference suggest using a microbe comprising a tetracycline resistance gene, and 7) the response cites a teaching by the Bostian et al reference that indicates a sub-inhibitory level of tetracycline can lead to a greatly increase level of expression from a tet resistance promoter.

With regard to the combination of references, applicants are correct to assume that the combination is Bostian et al in view of Setterstrom et al and further in view of Burnham et al or Nesin et al.

The examiner provided a motivation to combine the Bostian et al and Setterstrom et al references which is that it would be desirable, as exemplified by Setterstrom et al, to be able to compare the levels of infection in animals in which no pathogen target genes have been inactivated to levels of infection in animals in which a pathogen target gene has been selectively inactivated. The Setterstrom et al reference is supplied to demonstrate that the concept of using a control animal in infection studies was known in the art at the time of invention. Setterstrom et al is analogous to the teachings of Bostian et al in that it features the use of S. aureus infections in an animal model that is also taught by Bostian et al as applicable to their system for characterizing the genes of a pathogen. While the two references differ in their use of tetracycline in their systems (e.g. Setterstrom et al use it as an antibiotic itself, Bostian et al use it as a "switch" for regulating expression of a target gene in the pathogen), both systems are designed to determine the levels of infection in response to administration of the antibiotic. The system taught by Bostian et al, as well as by applicants, is designed to mimic the effects of a drug compound on infection based upon the inactivation of an essential gene within the pathogen

during infection. The key points here are that 1) Setterstrom et al is analogous art, and 2) Setterstrom et al establish the general level of knowledge in the art for using a control in studies where one looks at the level of infection by a microbe in a host animal in response to treatment with a drug. Applicants appear to be arguing that the use of control animals in such infection assays was somehow novel in the art at the time of the invention. This cannot be considered to be the case in view of Setterstrom et al. It would have been *prima facie* obvious to one of skill in the art to use a control animal in the methods taught by Bostian et al in order to provide a clear contrast between treated animals (i.e. where a specific pathogen gene was inactivated) and nontreated animals (no pathogen genes were inactivated) so that any effects observed in the treated animals could be clearly attributed to gene inactivation and not some other unknown factor.

With regard to the assertion that Bostian et al and Setterstrom et al do not teach the limitation of two groups wherein the first group is exposed to tetracycline throughout the entire course of the assay and wherein the second group is only initially exposed to tetracycline, this assertion is inaccurate. As clearly indicated in the rejection, Bostian et al teach a number of different constructs for regulating the expression of a target gene in the pathogen where the level of the switching compound (e.g. tetracycline) is removed or decreased (e.g. page 26, lines 14-31). In such a situation, the level of expression in the control animals, depending on the expression construct, would be controlled by not removing tetracycline. Thus, the teachings of Bostian et al and Setterstrom et al do teach this limitation of removing tetracycline from one of the populations of animals.

With regard to the asserted teachings of Bostian et al concerning "sub-inhibitory" levels of tetracycline, the response appears to be arguing that Bostian et al teaches exclusively the use of "sub-inhibitory" levels of tetracycline and that one would not be motivated based on these teachings to include a tetracycline resistance gene in the Bostian et al system. This appears to be a "teaching away" argument of sorts. First, there is no indication that including a tetracycline resistance gene as taught by Burnham et al or Nesin et al would cause the system taught by Bostian et al to not work, which would be a true "teaching away" from the claimed invention. Second, the inclusion of such a resistance marker would seem to be an excellent way, if one wanted to, of keeping the levels of tetracycline in the cell at levels that do not seriously affect cell growth during infection.

With regard to a lack of suggestion by the teachings of Bostian et al or Setterstrom et al concerning the presence of a tetracycline resistance gene in the host cells of the invention, this assertion is also inaccurate. Bostian et al teach it is desirable to use in their invention a genetically altered microbe that is resistant to the compound used as a "switching compound" in order to avoid confusion over interpretation of the experimental results (e.g. see page 18, first paragraph of Bostian et al). Bostian et al exemplify tetracycline as a preferred "switching compound" in their invention. Thus, Bostian et al provides sufficient motivation for one to combine the teachings of Burnham et al or Nesin et al with its teachings to make the system that is recited by the rejected claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
June 15, 2003